Armed Forces College of Medicine

AFCM

Septic and aseptic Meningitis

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INTENDED LEARNING OBJECTIVES (ILO)

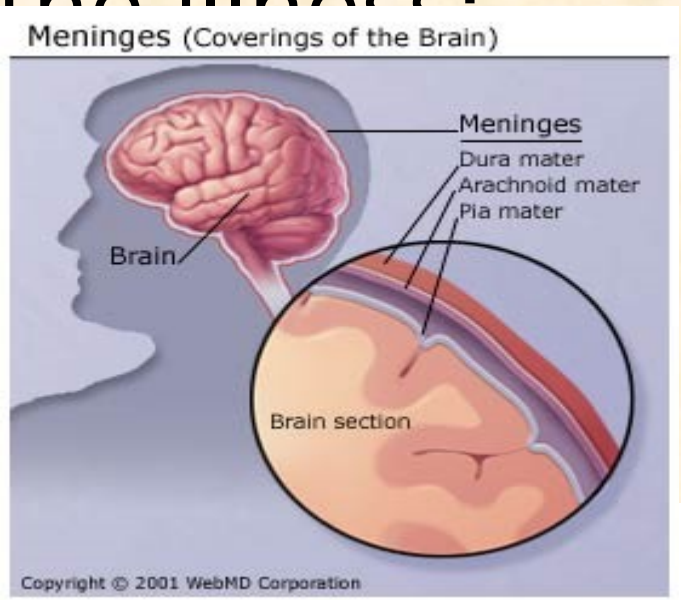
- **By the end of this session the student will be able to:**
- Describe the structure of viruses causing meningitis
- Describe pathogenesis and clinical manifestations of meningitis & encephalitis
- Outline laboratory diagnosis of meningitis & encephalitis
- Outline prevention and control of meningitis & encephalitis

Definition

- Meningitis is an infection of the meninges, the membranes that line the brain and spinal cord .

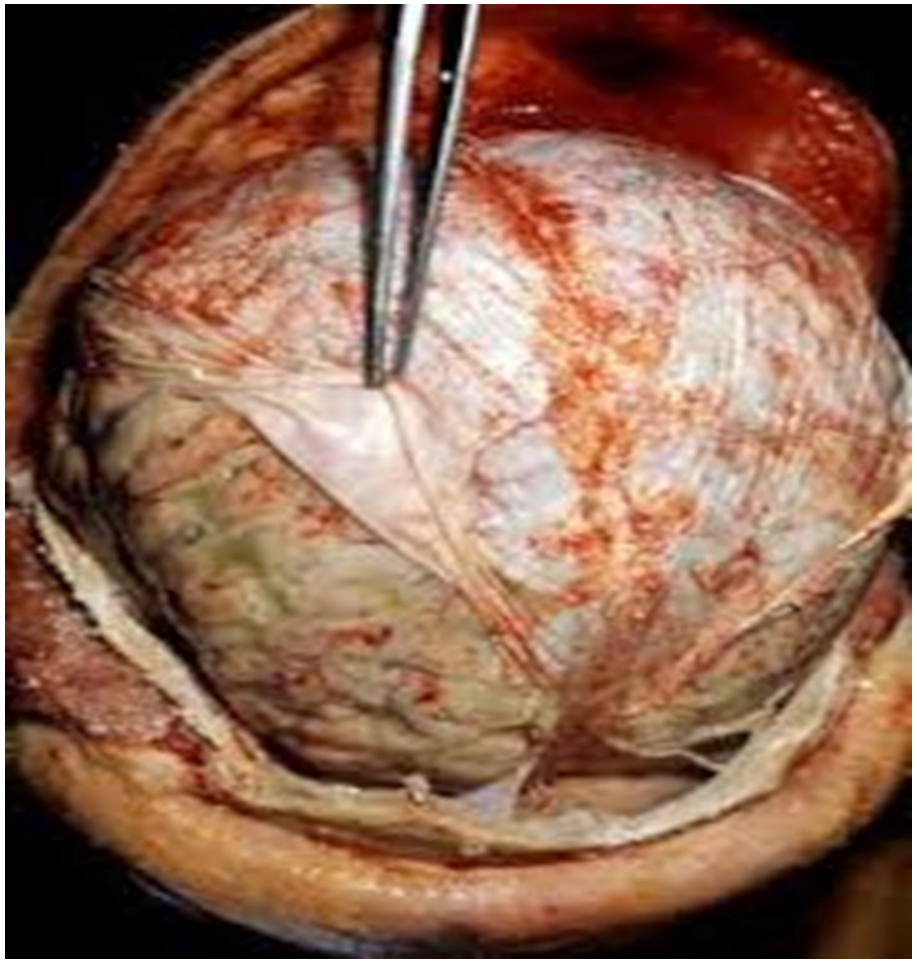
Depending on speed of the initial presentation and the rate of progression of the illness: Meningitis can be categorized

- Acute
- Subacute
- Chronic



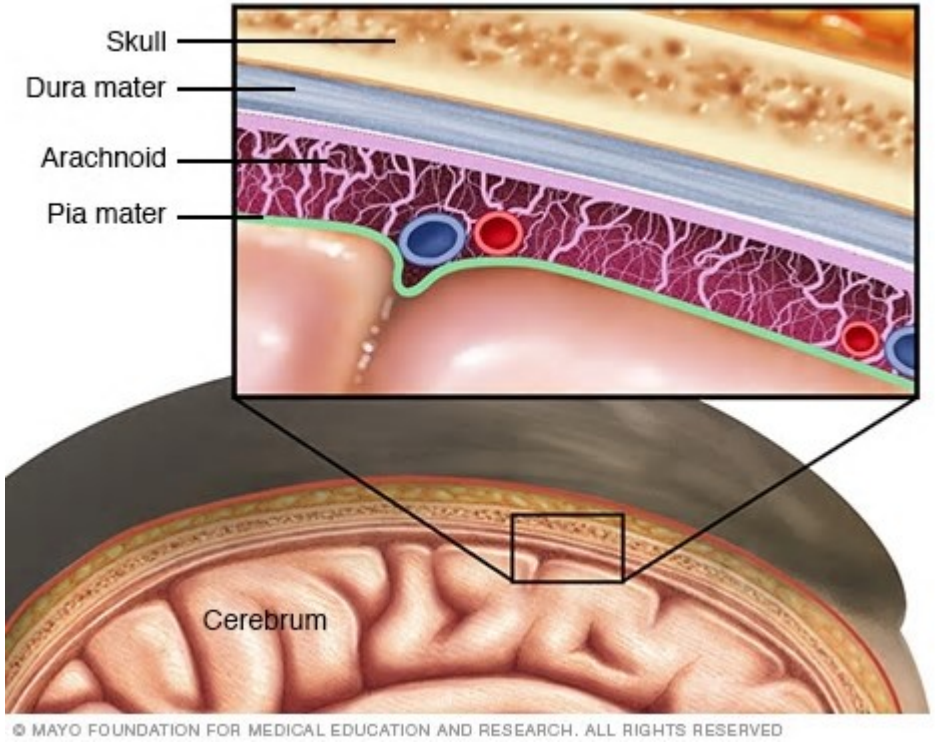
Septic Vs Aseptic

- ✓ Acute meningitis is caused by either pyogenic bacteria, such as *Streptococcus pneumoniae and Neisseria meningitidis*, or viruses, such as Coxsackie virus and herpes simplex virus type 2.
- ✓ Viral meningitis is often called aseptic meningitis because routine cultures for bacterial pathogens are negative.



Subacute meningitis

Subacute meningitis is caused by Mycobacterium tuberculosis and fungi, such as Cryptococcus. The causative organisms are often found in the spinal fluid located in the subarachnoid space.



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Viral (aseptic) meningitis

Origin of name	**No bacteria are involved**
Frequency	**The most common form of meningitis except in children< 5 years** where bacterial meningitis is more common
Etiology	**A- Entero viruses : Coxsackie – ECHO - Poliovirus** **B- Herpesviruses** : Herpes simplex virus-2 - Varicella zoster virus **C-Flavivirus** : West Nile virus (WNV) **D- Paramyxoviruses** : mumps virus
Signs & symptoms	Same as those of bacterial & fungal meningitis ,but a-Milder Rarely cause death b-Can be associated with skin rash, sore throat & colds
Outcome	1-Clinical course is **less fulminant** compared to bacterial meningitis 2- Infants <1 years : higher incidence of **speech & language delay**

Laboratory diag.	
A-Specimens	•Throat washing (in first few days) • Stools (for weeks) •CSF
B- RT-PCR	**RNA detection in CSF is the most sensitive and specific method**
Control **CSF analysis**	A - No avallable antiviral drugs B- IV Immunoglobulins (efficacy is uncertain) 1.Treatment of and to prevent outbreaks, 2.Neonatal Infections 3.Severe infections in immunocompromised individuals.

Virus	Sensibility (%)	Specificity (%)
HSV 1	>95	100
CMV	80-100	75-100
VZV		100
EBV	97	100
JC virus	74-92	92-96
Enterovirus	97	100

Etiology	Pressure (mm H_2O)	Cells (µL)	Proteins (mg/100 cc)	Glucose (CSF/blood)
Normal	<200	0–5 Lymphs, 0 Polys	<45	>0.6
Acute bacterial	Increased	200–5000; mostly (>90%) Polys	>100	<0.6
Acute viral	Slight increase	100–700 Lymphs	Slight increase	Normal

ENTEROVIRUSES

Structure

A-Family

Picorna (small RNA) viruses (together with Rhinoviru

B-Nucleocapsid

1-ss RNA 2- Icosahedral

C- Non enveloped

Members & Classification

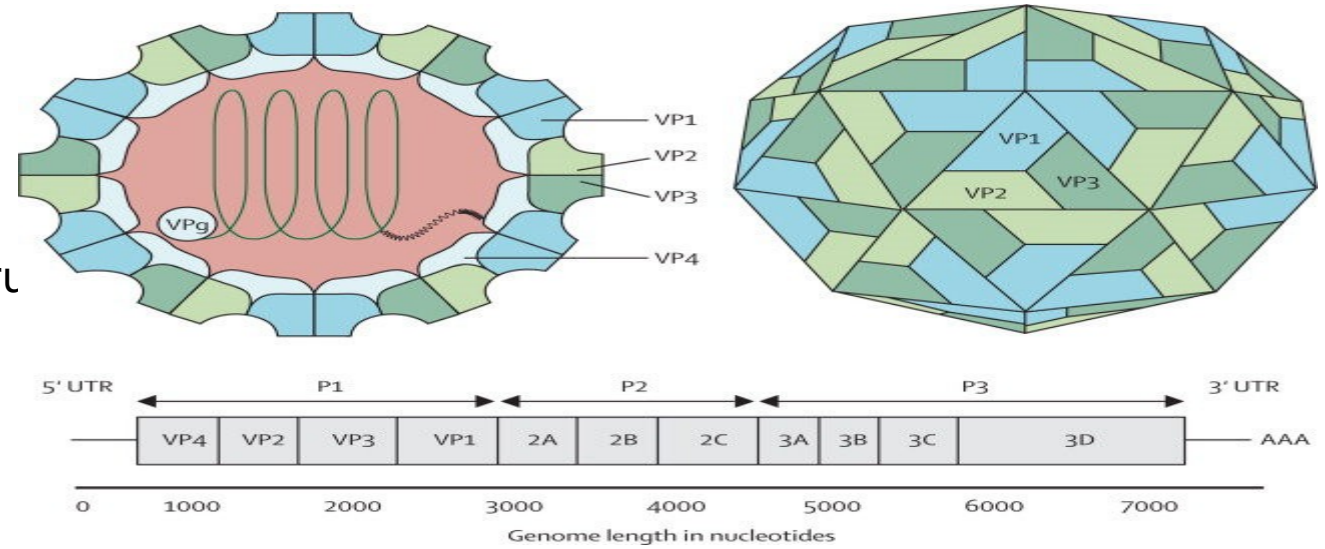
A-Polioviruses types 1 → 3.

B-Coxsackieviruses : Cox A (1-22 ,24) & Cox B (1-6)

C-ECHO viruses types 1-34

D- Enteroviruses types 68-71.

E- Heparnavirus (enterovirus 72) = hepatitis A virus (H



CATAGORIES OF ENTEROVIRUSES

VIRUS	SEROTYPES	CLINICAL DISEASES
Polioviruses	3 types	Asymptomatic infection, viral meningitis, paralytic disease, poliomyelitis
Coxsackie A viruses	23 types (A1-A22, A24)	Viral meningitis plus, rash, ARD, myocarditis, orchitis
Coxsackie B viruses	6 types (B1-B6)	Viral meningitis, but no orchitis
Echoviruses	34types	Viral meningitis, with orchitis
Other Enteroviruses	4 types(68-71)	Viral meningitis By 71

ENTEROVIRUSES

Pathogenesis

A-Modes of transmission : primarily in the summer and fall.

1 -Fecal-oral : main route

Replicate in the oropharynx and the intestinal tract.

2-Respiratory aerosols (droplet) : for Coxsackie viruses

B-Site of replication :

Primarily in GIT due to :

1-Optimal replication at **37C**

2-Stable under acid conditions (pH3-5) => survive exposure t

C-Members causing **aseptic meningitis**

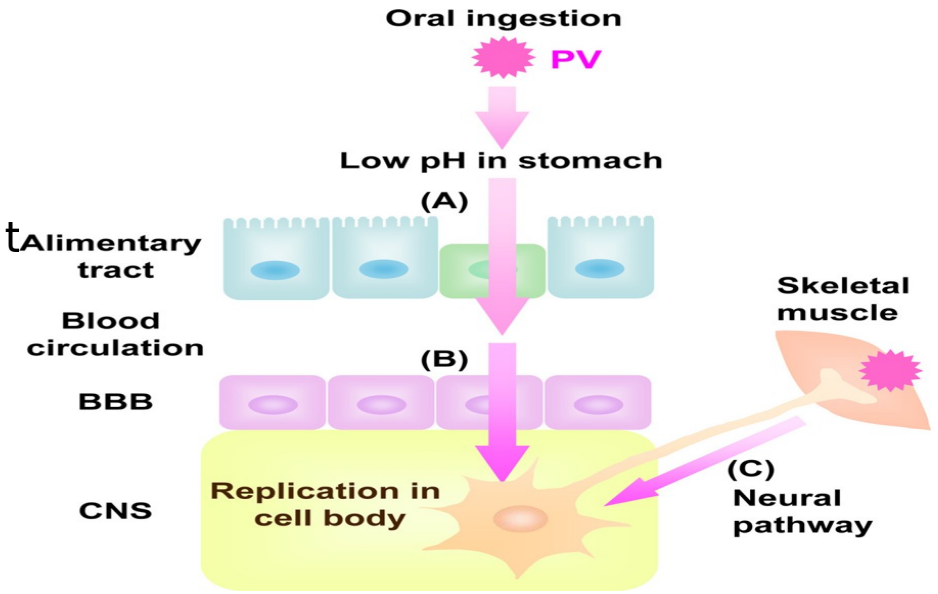
1- Coxsackieviruses & ECHOviruses (commonest causes)

2-Polio viruses

3-Enterovirus type 71

TRANSMISSION OF ENTEROVIRUSES

- Fecal – oral route: poor hygiene, dirty diapers(especially in day-care settings)
- Ingestion via contaminated food and water
- Contact with infected hands
- Inhalation of infectious aerosols



Polioviruses

Structure

A-Family

Picorna viruses

B-Nucleocapsid

1-ss RNA

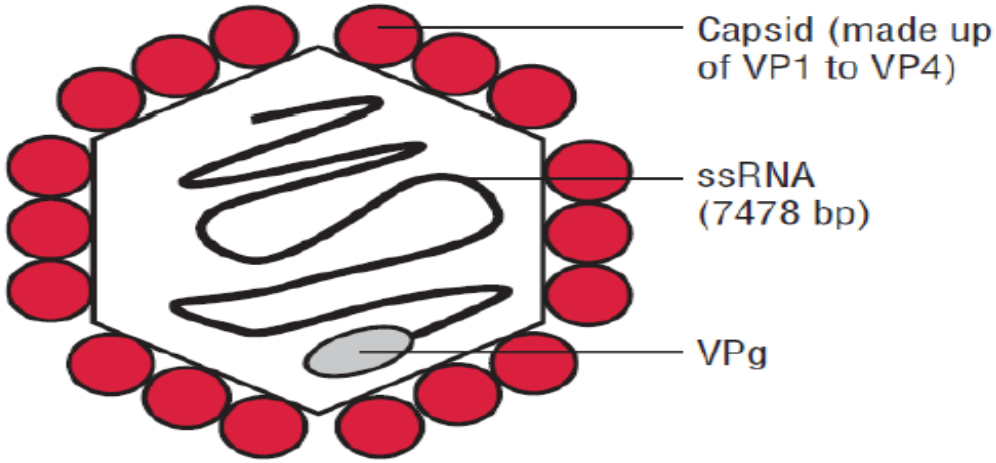
2- Icosahedral

C- Non enveloped

D - Classification

3 serotypes

based on differences in the **outer capsid proteins**



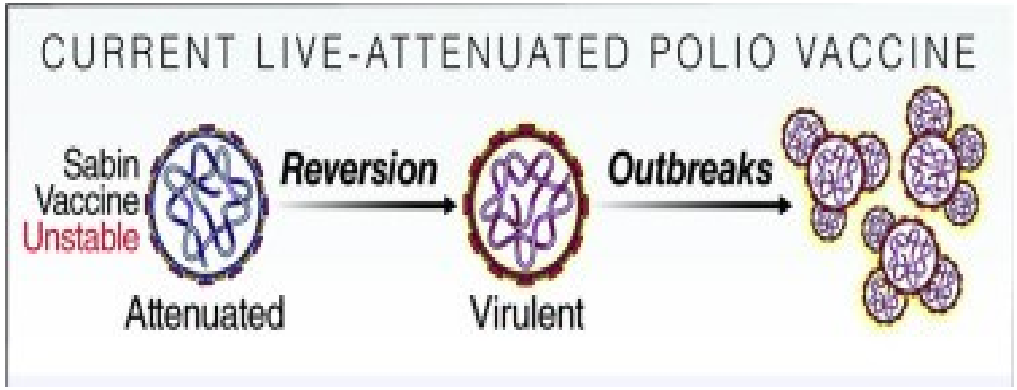
Antigenic properties

- **Based on Neutralisation test**
- Poliovirus (PV) classified into 3 types: Type 1, Type 2 & Type 3
- Prototype strains:
  - ➢Brunhilde & Mahoney strains for Type 1
  - ➢Lansing and MEFI for Type 2
  - ➢Leon and Saukett for Type 3

Type 1 Most common, causes most epidemics
Type 2 Usually cause endemic disease
Type 3 Strains cause epidemic.

Polioviruses

Epidemiology



A-In Western Hemisphere

- **Poliomyelitis caused by natural " wild-type" virus was eradicated due to successful vaccines**
- **Rare cases occur mainly in:**

a-People exposed to **virulent revertants** of the attenuated virus in th

b-**Unimmunized people** exposed to **wild-type** poliovirus while **trave**

- 350,000 cases
- 125 endemic countries
- World Health Assembly voted to eradicate polio

- 34 cases reported*
- 3 endemic countries

B-In developing countries

- WHO set the eradication of paralytic polio by 2005 as a goa**l.**
- This goal wasn't achieved **as of 2012,** there was 200 cases each ye

Afghanistan, Nigeria & Pakistan

Polioviruses

Pathogenesis

A- Soure of infection

Apparent and subclinical patients.

B-Phases

1- Alimentary phase

1ry multiplication takes place in **oropharynx** & **intestinal** mucosa

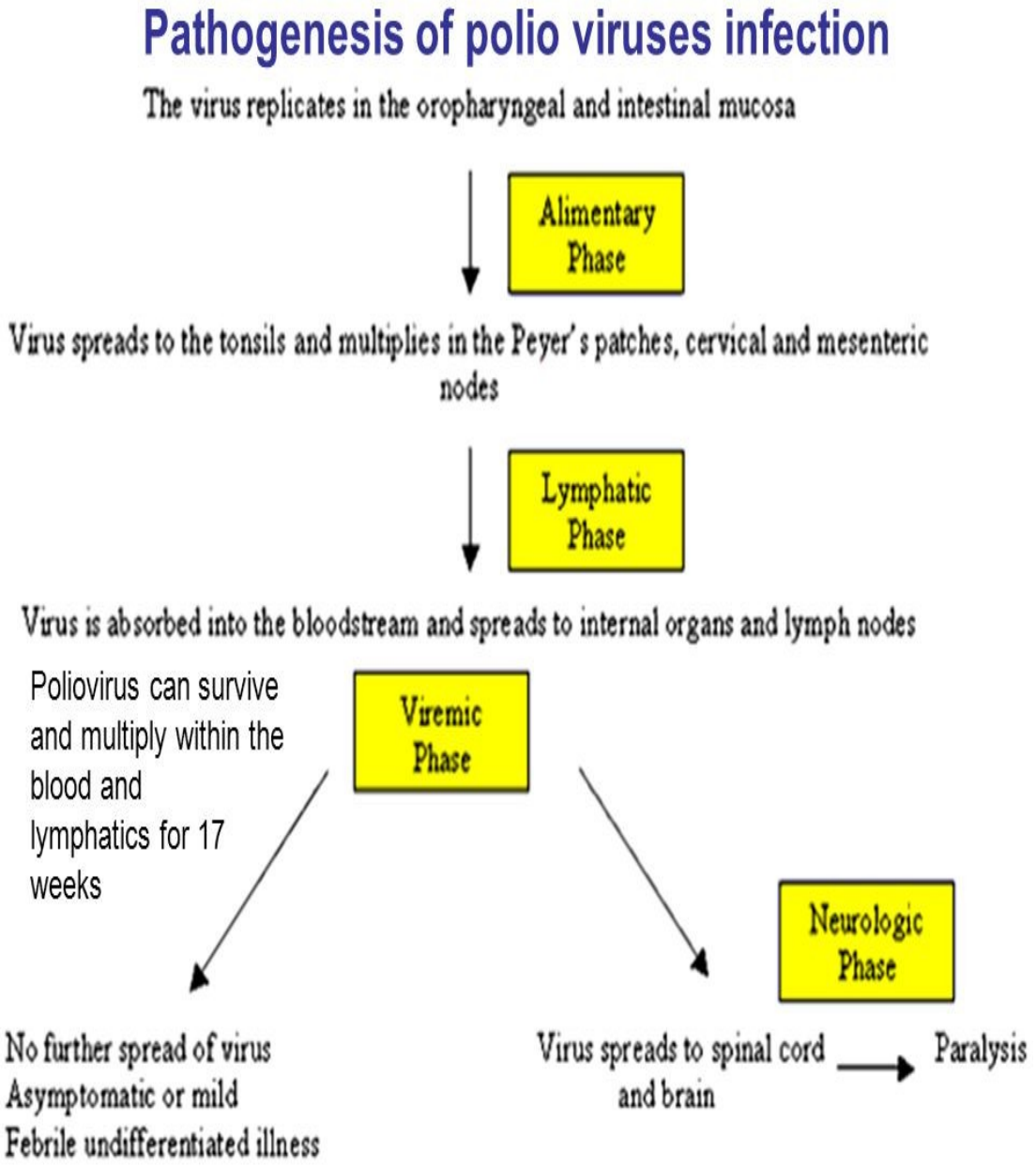
2- Lymphatic phase

The virus then multiplies in **tonsils** & **Payer's patches**

Most infections stop at this level (asymptomatic or subclinical).

3-Viremic phase : viremia occurs

Neutralizing Abs may stop progression of disease **(abortive polio)**


Pathogenesis of polio viruses infection
The virus replicates in the oropharyngeal and intestinal mucosa
Alimentary Phase
Virus spreads to the tonsils and multiplies in the Peyer's patches, cervical and mesenteric nodes
Lymphatic Phase
Virus is absorbed into the bloodstream and spreads to internal organs and lymph nodes
Poliovirus can survive and multiply within the blood and lymphatics for 17 weeks
Viremic Phase
Neurologic Phase
No further spread of virus
Asymptomatic or mild
Febrile undifferentiated illness
Virus spreads to spinal cord and brain
Paralysis

Polioviruses

4

Nervous system may be invaded through **the blood stream**

- **Aseptic meningitis or non-paralytic polio**

Virus reach the meninges

- **Paralytic polio**

a- Virus spread along **axons of peripheral nerves of CNS (AHCs of spinal cord)**

Multiplication

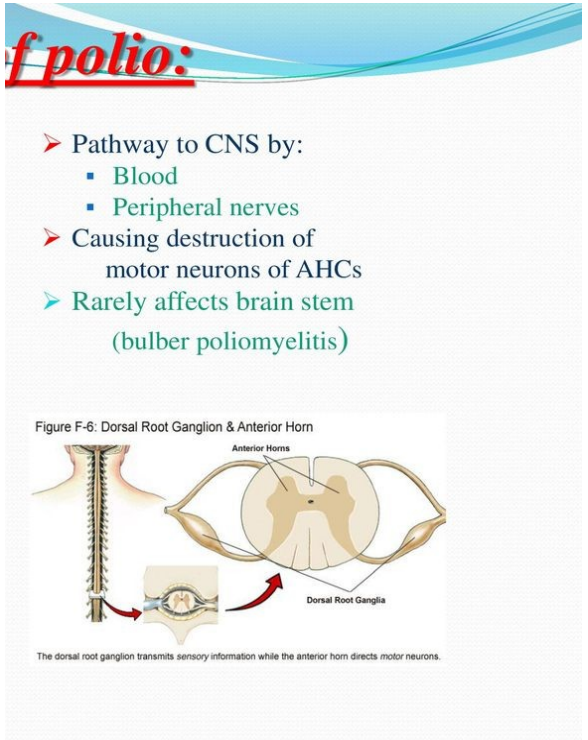
Death of cells

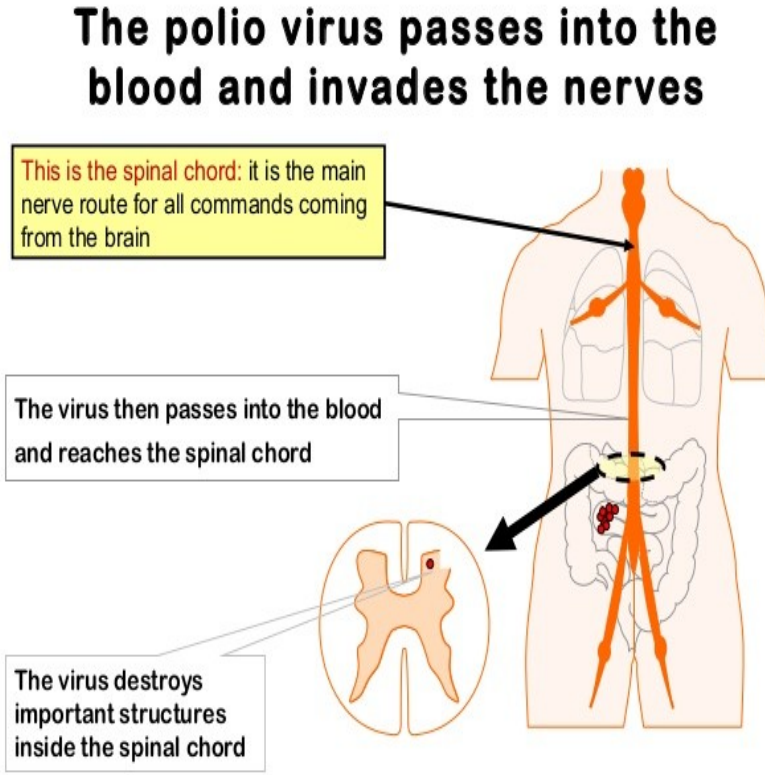
b- Predisposing factors

Tonsillectomy in child with inapparent infection in **nasopharynx**

Virus enters **cut nerve fibers**

c- Virus may affect the brain stem


f polio:
Pathway to CNS by:
Blood
Peripheral nerves
Causing destruction of motor neurons of AHCs
Rarely affects brain stem (bulber poliomyelitis)
Figure F-6: Dorsal Root Ganglion & Anterior Horn
Anterior Horns
Dorsal Root Ganglia
The dorsal root ganglion transmits sensory information while the anterior horn directs motor neurons.


The polio virus passes into the blood and invades the nerves
This is the spinal chord: it is the main nerve route for all commands coming from the brain
The virus then passes into the blood and reaches the spinal chord
The virus destroys important structures inside the spinal chord

C-Immunity

1- Intestinal secretory IgA

2- Humoral IgG to the specific serotype

Infection provides **lifelong type- specific immunity**,

but does not confer immunity to other serotypes

⬇

(No cross protection)

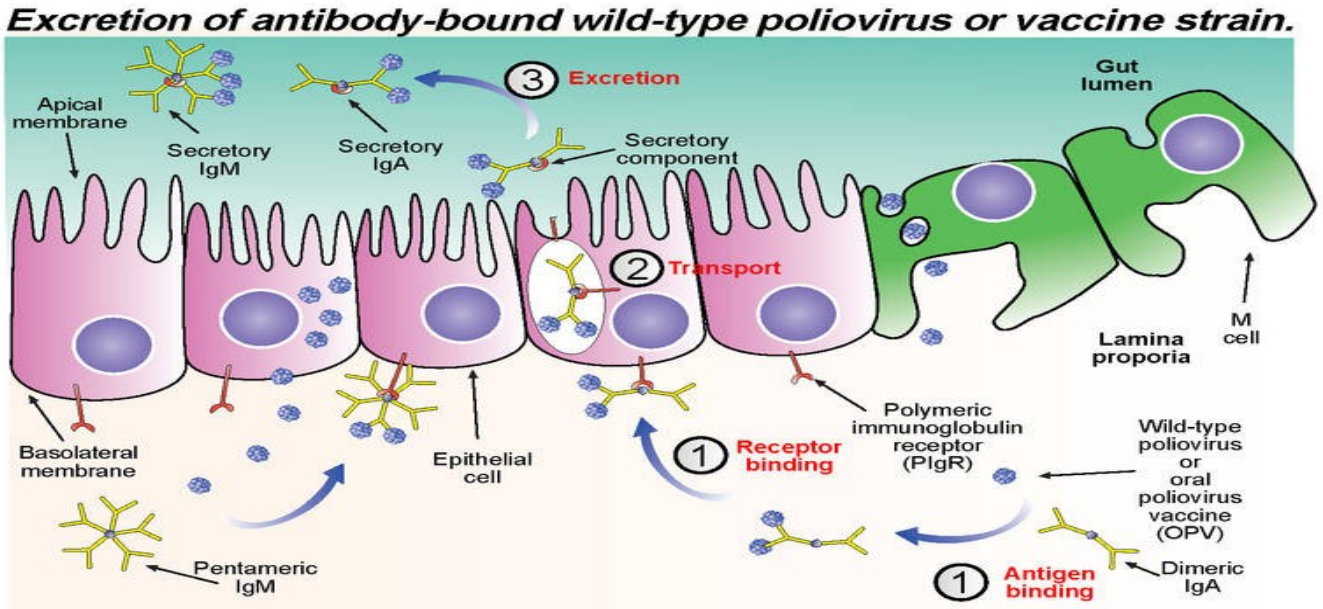
Vaccine must contain the 3 serotypes

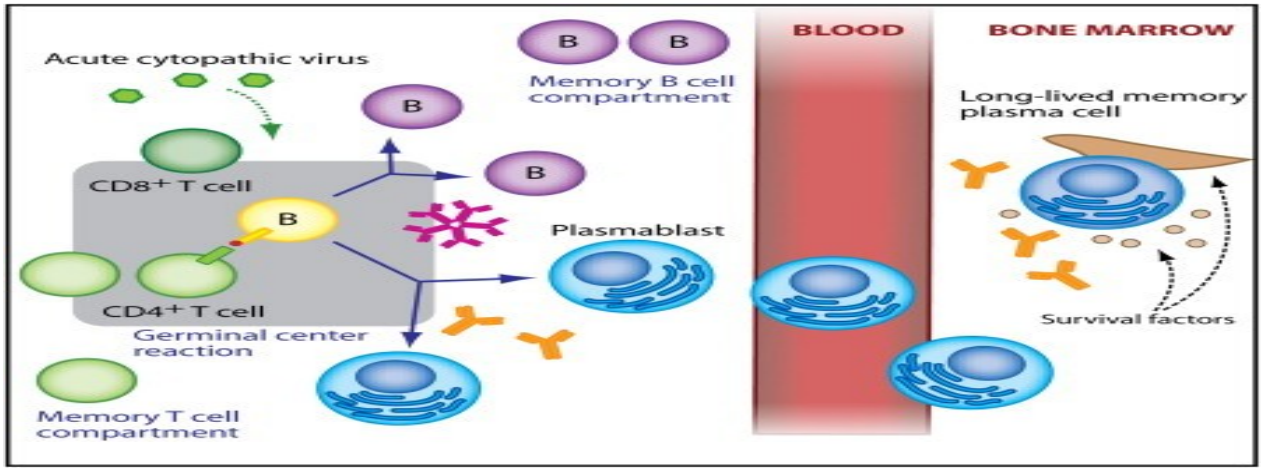
3- Maternal IgG cross the placenta

Passive immunity to newborns

⬇

⬇





Serotypes

Specificity to receptor restricts mutation rate; slow genetic drift

Three serotypes with no cross immunity

- Type 1 polio 90%
  Weakest, only 1% causes neuroparalysis
- Type 2 polio 9% (Eliminated)
- Type 3 polio 1%
  Greater temperature stability

Requires trivalent polio vaccine

Clinical Manifestations

1- Asymptomatic (subclinical) infection

2- Abortive polio : **Most common symptomatic** form

Fever, abdominal pain ,vomiting & constipation

3-Non Paralytic polio (aseptic meningitis)

Fever ,neck stiffness & pain **Complete recovery**

4-Paralytic polio : < 1% of infections

a -Flaccid paralysis : predominant complain

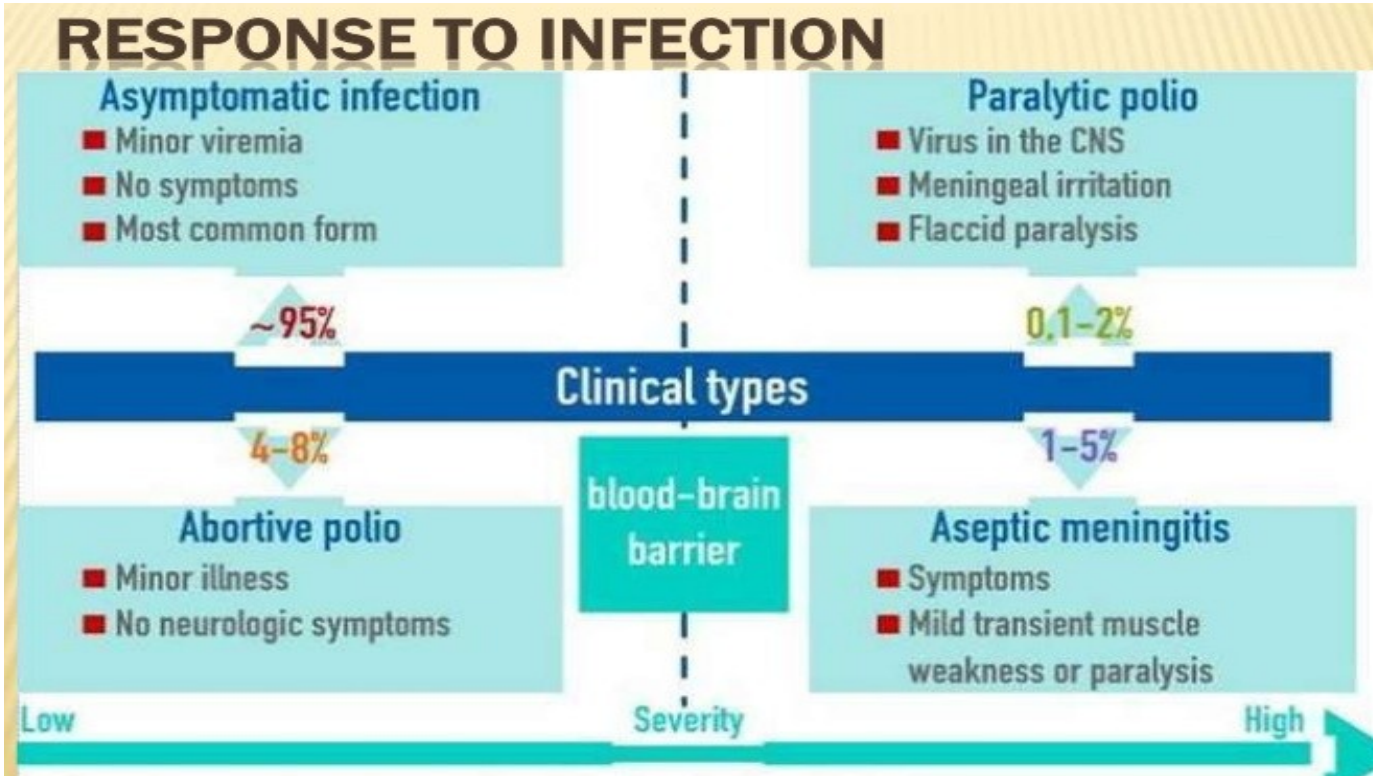
Post poliomyelitis muscle atrophy due to nerve supply affection

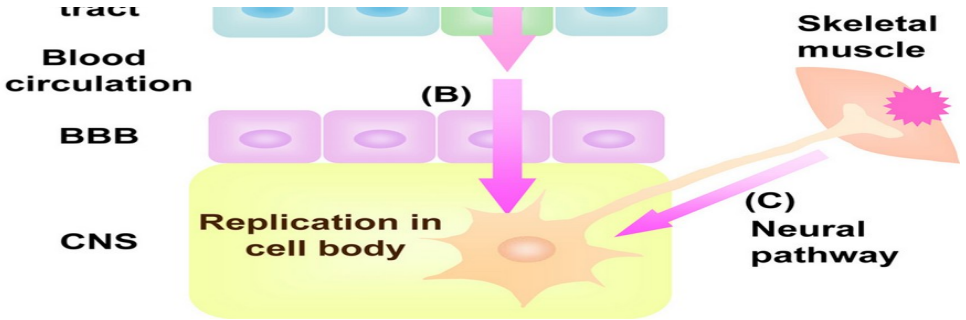
(muscle itself isn't affected)

b-Fatal respiratory paralysis in brain stem infection

No permanent carrier state occurs following infection by poliovirus,

but virus excretion in the feces can occur for several months.





Polioviruses

Laboratory diagnosis

A-Specimen	**1-Throat swab :** early **2-Stools :**late **3-CSF :** in meningitis
B-Direct demonstration of virus	RT-PCR : detects RNA **Rapid diagnosis of meningitis**
C-Isolation of virus	On human or monkey kidney tissue culture (MKTC) **CPE** ● Serotyping by **addition of monoclonal**

Poliovirus

- Diagnostic & Management strategy of Case scenarion:
- **Throat swab, Stool, CSF** sent to Diagnostic Microbiology Dept. for viral studies
- Throat swab and stool specimen tested positive for **Cytopathic effect (CPE) in tissue culture.**
- Virus was confirmed as Poliovirus type 1 by **Neutralization test**
- **Reverse Transcriptase PCR** was positive for Poliovirus in CSF

Polioviruses

Prevention

I-Active immunization

Two types of vaccines:

✓**Killed vaccine (Salk vaccine, inactivated vaccine, IPV) and**

✓ **Live attenuated vaccine (Sabin vaccine, oral vaccine, OPV)**

II-Passive immunization

Gamma globulins

Given shortly **before infection** or before nervous lesions

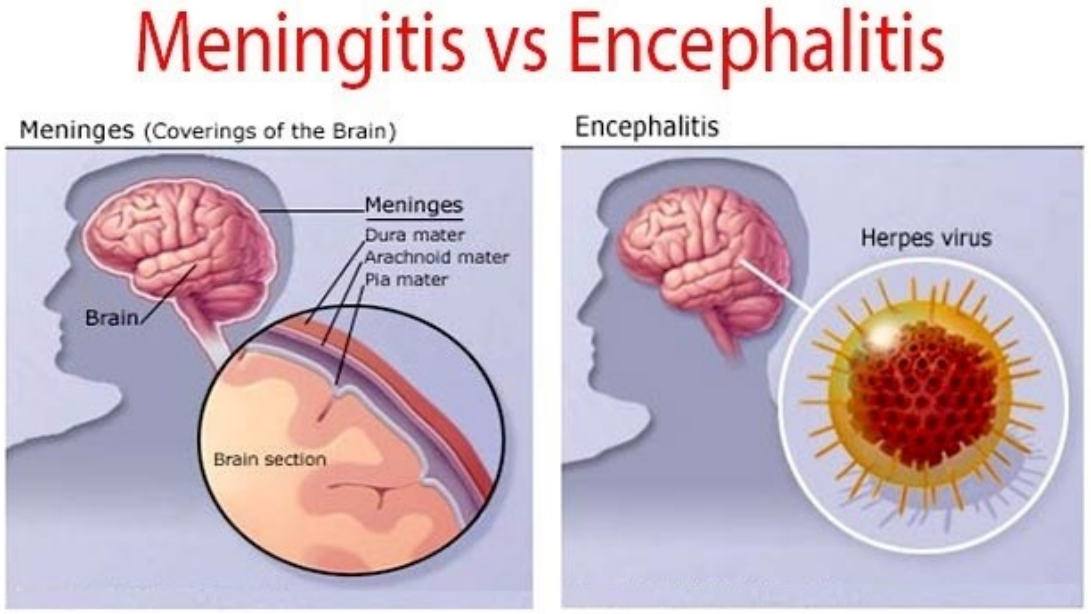
Prevent paralysis

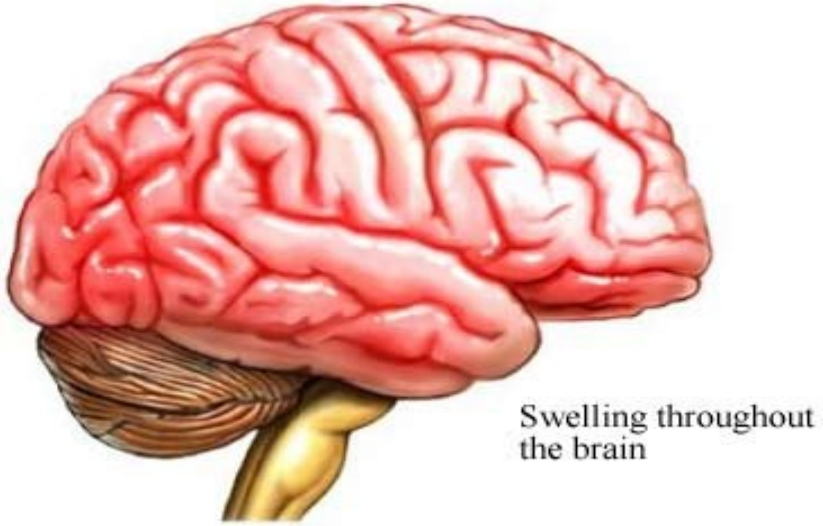
Oral polio vaccine (OPV):Sabin (1957)	Inactivated polio vaccine (IPV):Salk (1954)
A - Contents & Preparation	
3 serotypes grown on human or monkey cell culture →	3 doses given at 2 , 4 & 6 ms
B - Effects	
Induce systemic Abs **: IgG&IgM** → Neutralization of virus → **(100%)**	**Protection of CNS from wild virus**
C - Advantages : Live attenuated	**C - Disadvantages : Killed (by formalin)**
1 - Booster dose at 4-6 yrs (No need for repeated boosters)	1-Confer immunity **after 4 booster doses**
2-Oral → **Multiplication in intestine** → **GIT protection** → **sIgA**	2-IM → **No sIgA**
3- Production of herd immunity **Attenuated virus passes in stools of vaccinated children** **Infects & provides immunity for non vaccinated children**	**3-No herd immunity**

Oral polio vaccine (OPV):Sabin (1957)	Inactivated polio vaccine (IPV) : Salk (1954)
D - Disadvantages : Live attenuated	**D- Advantages : Killed**
1-Contraindicated in immunodeficient patients	**1-Safe administration** in immunodeficient patients
2-Can mutate to more virulent strain → Risk of vaccine-associated poliomyelitis in vaccine recipients or contacts	2-No reversion to virulence
3-Interference → Its replication & immunity is interfered if another enterovirus is infecting the gut of the child → Not given to a feverish child	**3 - No interference**
4 - Must be kept refrigerated to avoid heat inactivation of the live virus.	**4-Stable**

Encephalitis & Meningoencephaliti

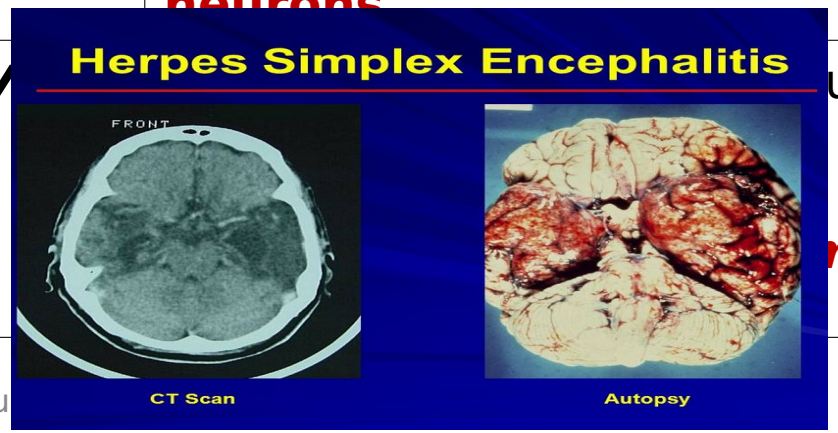
- **Encephalitis** is an infection of **the brain parenchyma**, most commonly caused by **VIRUSES**.
- **Meningoencephalitis** is an infection **of both** the brain and the

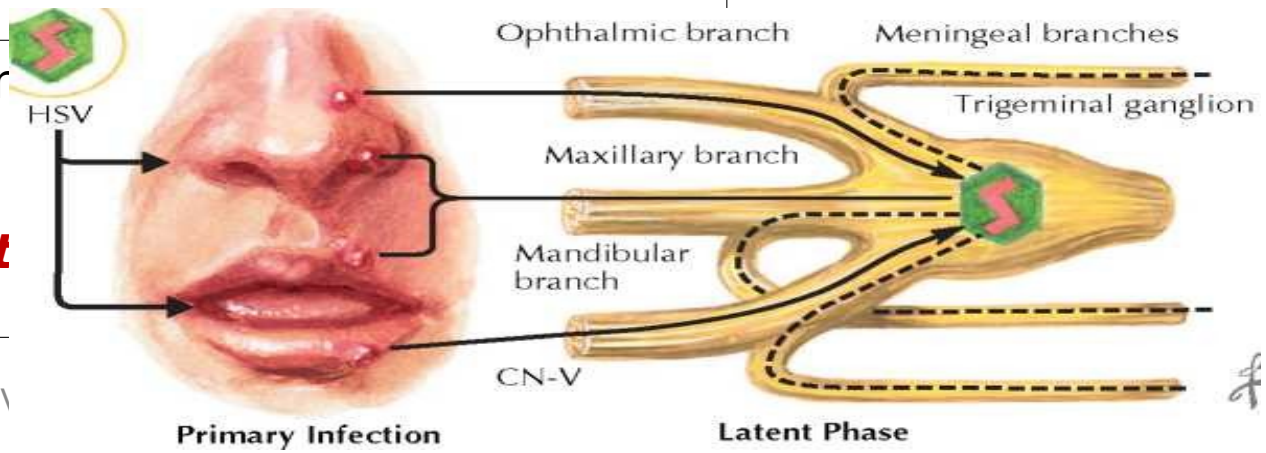




Encephalitis & Meningoencephaliti

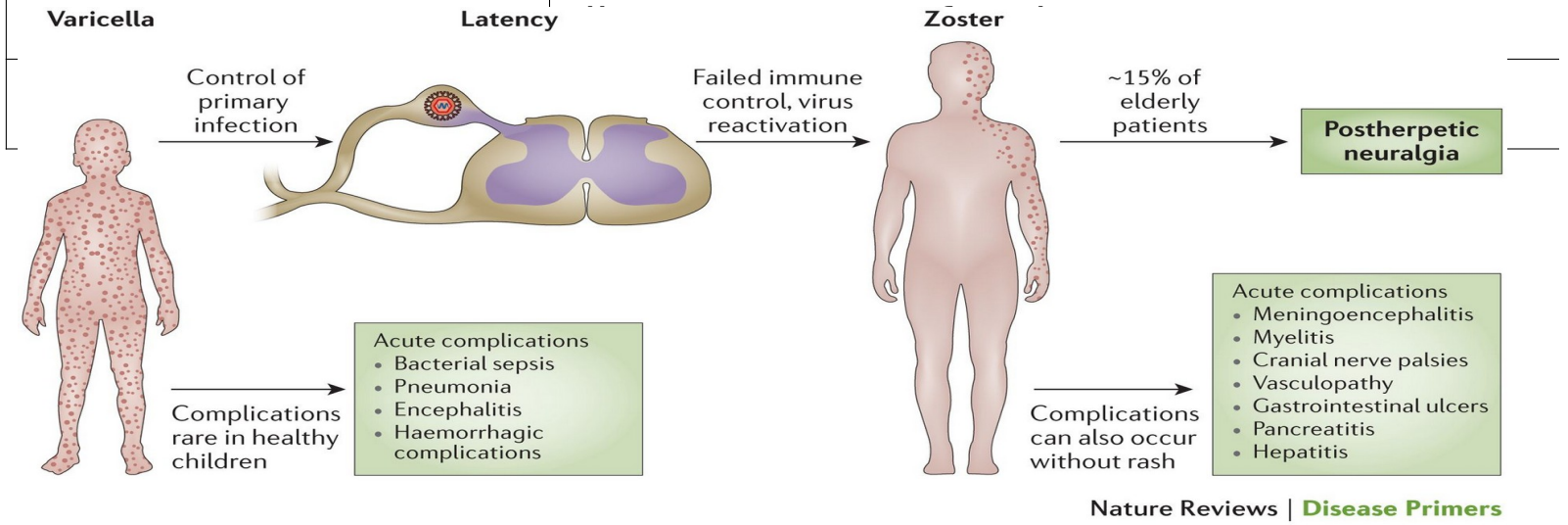
Etiology	Pathogenesis	Prevention
1- Herpes simplex	**The most common cause** of **severe meningoencephalitis** ⇓ Infection is localized to **the temporal lobes**	• **No vaccine** • Pregnant ♀ with active lesions late in pregnancy : receive
a-HSV-1	**Reactivation of latent infection** in the trigeminal ganglion ⇓ following **immunosuppression** in adults. ⇓ Reaches the temporal lobe by **travel down sensory neurons**	
b-HSV	urir ***mat***	

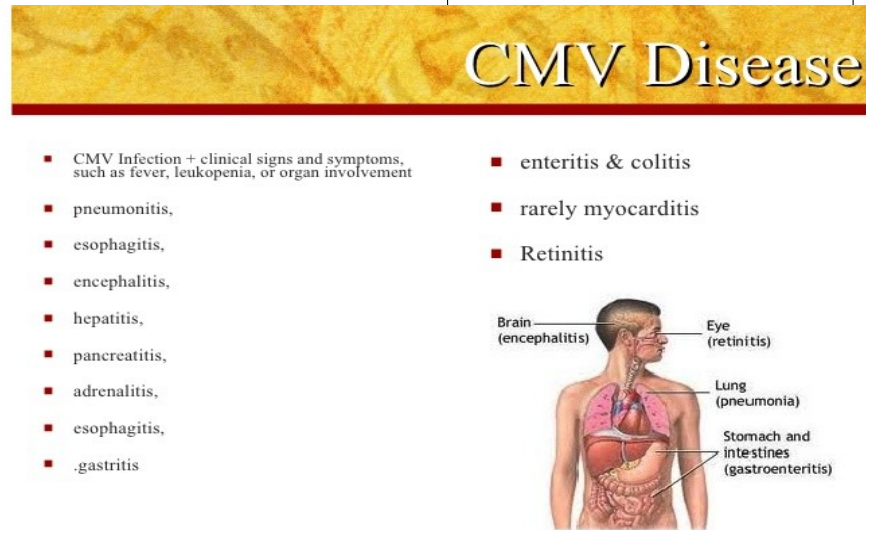




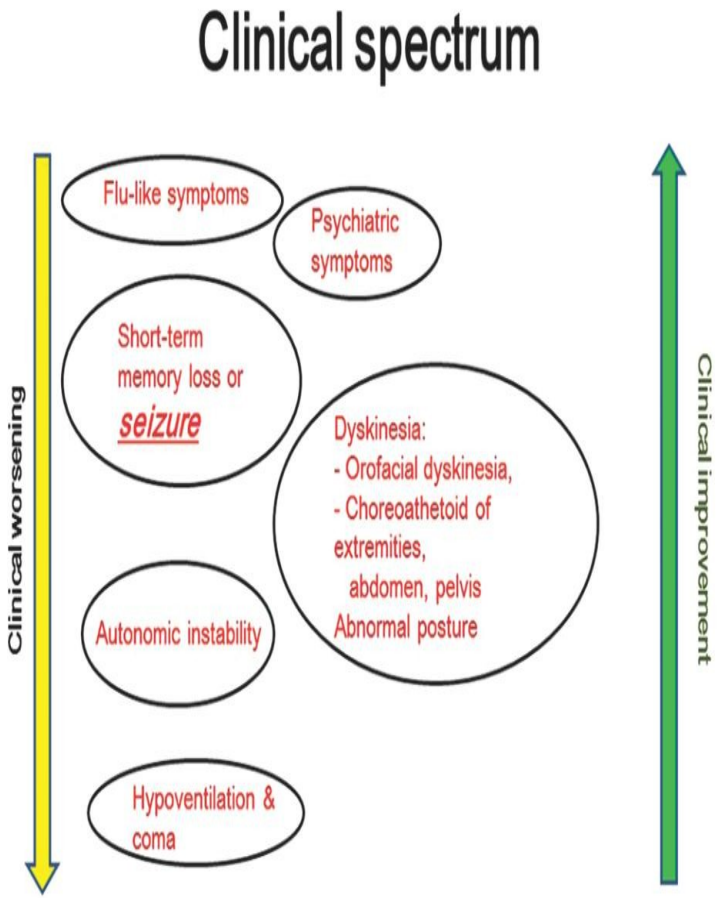
Encephalitis & Meningoencephalitis

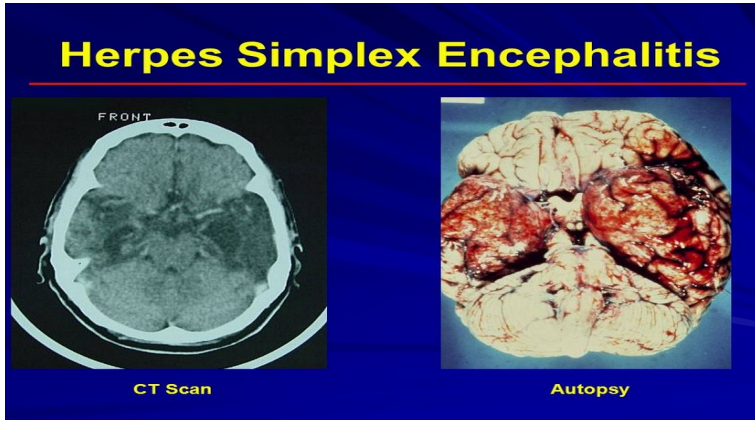
Etiology	Pathogenesis	Prevention
2 – Varicella - Zoster Virus	Encephalitis during the **primary infection (chickenpox)** or during the **reactivation infection (shingles).**	Varicella Zoster **vaccine**
3 - Cytomegalovirus	Encephalitis primarily in **immunocompromised individuals :** **a . AIDS** patients **b.**Those receiving **immunosuppressive drugs**	
4-Measles &Rubella	**Post infectious encephalitis :** occurs **shortly** after	**MMR** VACCINE





Clinical manifestions	Distinction between meningitis & encephalitis depends on the **state of brain function**
A - Encephalitis	1- Fever, headache **2- Altered mental status** :seizures and focal neurologic deficits.
B-HSV encephalitis	**Temporal lobe localization :** 1-Personality change 2- Hallucinations 3- Aphasia
Lab. diagnosis	
A- CSF analysis	**1- Mild ↑ in lymphocytes ,↑ protein &normal glucose**. **2- Normal CSF** pattern can also be seen **in encephalitis**





Suggested Text books

1. ***Review of Medical Microbiology and Immunology, Warren Levinson Chapter 67 p. 1298: 1307***

Thank you